

# Hypoglossal Nerve Stimulation for Obstructive Sleep Apnea: A Novel Surgical Approach (A Review of Literature)

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## ABSTRACT

**Introduction:** Obstructive sleep apnea (OSA) is associated with considerable health risks. Continuous positive airway pressure (CPAP) is the gold standard treatment, but its efficacy is reduced by inadequate adherence to treatment. Surgical treatment for OSA has evolved to neuromodulation with the advent of hypoglossal nerve stimulation.

**Objectives:** To evaluate the efficacy of hypoglossal nerve stimulation in the treatment of OSA syndrome.

**Methods:** Studies were included that evaluated the efficacy of hypoglossal nerve stimulation to treat OSA. Six prospective studies were included in this trial.

**Results:** Six studies with a total of 242 patients were included in this review. All the studies demonstrated a reduction in apnoea hypopnoea index (AHI), Oxygen desaturation index (ODI), and Epworth sleepiness scale (ESS). Despite using different hypoglossal nerve stimulators in each subgroup analysis, no significant difference was found in any of the comparisons, suggesting equivalent efficacy regardless of the system in use.

**Conclusion:** Hypoglossal nerve stimulation (HGNS) therapy has so far proved to be an effective alternative treatment of obstructive sleep apnea in CPAP intolerant selected group of patients.

**Keywords:** Continuous positive airway pressure, Hypoglossal nerve stimulation, Obstructive sleep apnea.

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## INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by repetitive upper airway collapse during sleep, causing hypoxemia and sleep fragmentation that leads to daytime sleepiness and increased risk of cardiovascular incidents, motor vehicle, and occupational accidents.<sup>1-3</sup>

The prevalence of sleep apnea in north India is 13.7%.<sup>4</sup> The gold standard for the treatment of OSA is CPAP.<sup>5</sup> It has been demonstrated that successful CPAP treatment improves systemic hypertension and prolongs survival.<sup>6</sup> However, the clinical effectiveness of CPAP is often limited by low patient acceptance, poor tolerance, and suboptimal compliance.<sup>7</sup> Therefore, non-CPAP alternatives for the treatment of sleep disordered breathing, such as oral appliance therapy with custom-made, titratable mandibular advancement devices, surgery, or upper airway stimulation (UAS) have gained growing interest.<sup>8-11</sup> UAS therapy, which uses electrical stimulation of the hypoglossal nerve, has been reported to be safe and efficacious in a select group of OSA patients who cannot or will not use CPAP as primary treatment.<sup>12,13</sup> In 1978, Remmers et al. were the first to report the direct relationship between loss of genioglossus muscle activation during sleep and upper airway closure in patients with OSA.<sup>14</sup> This finding led to early attempts to treat the disorder by electrical stimulation of the pharyngeal muscles with transcutaneous, intraoral and intramuscular electrodes.<sup>14-16</sup> Several subsequent projects since then have attempted to prove the usefulness of hypoglossal nerve stimulation (HGNS) as a novel therapeutic approach to sleep apnea.<sup>17</sup>

## Concepts of Hypoglossal Nerve Stimulation Devices

The clinical model of HGNS was first attempted at the Johns Hopkins University, and the study was completed in 2001.<sup>18</sup> Following the published technical limitations of this study, improvements took place; in 2011 three clinical trials were sponsored by different firms:

- Apnex (St. Paul, MN, USA)
- Inspire (Maple Grove, MN, USA)
- ImThera Medical (San Diego, CA, USA)

Inspire, and Apnex trials are based on unilateral stimulation of medial branch of the hypoglossal nerve with inspiration while in ImThera trial, the stimulus was given to the main trunk of the nerve and delivered at both inspiration and expiration, thereby excluding the need of an inspiratory sensor.<sup>13</sup>

The food and drug administration (FDA) approved device is Inspire-II. The star trail with large multicenter one-year phase 2 to 3 trial was completed in 2014. A total of 126 patients with inclusion criteria consisting of CPAP nonadherence, body mass index (BMI) < 32 kg/m<sup>2</sup>, AHI

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between 20 to 50 events/hour, the absence of complete concentric collapse (CCC) on drug-induced sleep endoscopy (DISE) at velum, central apnea were enrolled.<sup>19</sup> Inspire HGNS device requires DISE as a pre-requisite to surgical implantation because CCC is a predictor of non-response. The device consists of the single circumferential electrode lead placed around the medial division of XII nerve and the respiratory sensor placed in ipsilateral inter-costal space and a pulse generator.

The ImThera medical device is a modification which excludes the need of inspiratory sensors. This device consists of a pulse generator, and circumferential six electrode leads placed around the main trunk of hypoglossal nerve with cyclical stimulation of the nerve which obviates the need for synchronization with respiration.<sup>20</sup> As the device does not need a sensory lead, it does not require DISE prior to implantation. Inclusion criteria consisted of BMI between 25 and 40 kg/m<sup>2</sup>, AHI more than 20/hour, the modified Mallampatti score between 1 and 3. Currently, this is under phase-III trials.

Apnex system also had circumferential single electrode lead placed around the distal medial division of cranial nerve XII, respiratory sensors placed bilaterally in intercostal spaces and pulse generator in the ipsilateral infraclavicular pocket. The final cup placement on the nerve was based on an intra-operative response of upper airway to stimulation, visualized using fluoroscopy. Inclusion criteria were moderate to severe OSA patients with age 21 to 70 years, BMI ≤40 kg/m<sup>2</sup>, AHI of 20 to 100 events/hour and all subjects to have a predominance of hypopnea ≥ 80% of the sum of apnea and hypopnea events. Even though the 6 months follow-up yielded better results, the larger scale phase 2 to 3 trials did not deliver anticipated results. The procedure-related adverse events at 12 months were found to be 71%. Surgically unsuccessful results led to the cessation of device development.<sup>21</sup>

### Surgical Procedure

The implantation procedure is done under general anesthesia. A 5 cm incision is made one fingerbreadth below the mandibular margin, anteriorly up to midline and posteriorly to the submandibular gland. Dissection is done to identify the hypoglossal nerve. The digastric tendon is identified and retracted inferiorly while submandibular gland is lifted posterosuperiorly. Mylohyoid muscle is identified, and the posterior edge is retracted anteriorly to identify the main trunk of the hypoglossal nerve, which is then traced anteriorly. The medial and lateral branches are identified and confirmed using a nerve integrity monitoring system ((NIM, Medtronic Xome®),<sup>22</sup> and the cuff selectively wraps around the medial branches in Inspire II, while in the ImThera Medical Inc the electrode cuff is rolled under and around the main trunk of the nerve.<sup>20</sup>

The pleural pressure sensing lead is placed through a horizontal incision that is made at the right fourth or fifth intercostal space lateral to the nipple line. Dissection is carried out to the upper border of the underlying rib, and a pocket is tunneled postero-anteriorly between external and internal intercostal muscle layers where the sensing lead faces pleura.<sup>23</sup>

The implantable pulse generator (IPG) connects the nerve stimulation cuff and the pleural sensing electrode. A subcutaneous pectoral pocket is created 2 to 5 cm inferior to the right clavicle and medial to the deltopectoral groove. Inferiorly the pocket is extended subcutaneously to the pleural sensing electrode. Superiorly, a subplatysmal tunnel is created to the hypoglossal nerve stimulation cuff, and the lead passed downwards and connected to (IPG). After the implantation of the HGNS system, the electrical integrity is confirmed, and the IPG is tested to confirm tongue protrusion.

### Stimulation Protocol

The Inspire II system is activated 4 weeks post-implantation, and the stimulation is given between end expiration through the inspiratory period to minimize neuromuscular fatigue.<sup>24</sup> Titrations are performed at 1, 2 and 4 months postimplantation.

The ImThera medical system is activated in seated awake patients 3 to 4 weeks after surgery.<sup>20</sup> Electrodes are stimulated cyclically in a pattern independent of the respiratory cycle and titrations performed at 1 and 12 months postimplantation.

### OBJECTIVES

To evaluate the efficacy of hypoglossal nerve stimulation in the treatment of OSA syndrome as a novel surgical technique.

### METHODS

Studies were included that evaluated the efficacy of hypoglossal nerve stimulation to treat OSA. Six prospective studies were included in this trial.

Study	Study design	Device used	Sample size	Findings
Eastwood et al. <sup>25</sup>	Prospective single-arm interventional trial	Apnex (Medical Inc.)	21	Improvement in AHI from 43.1 events/hour to 19.5 events/hour Improvement in ESS from 12.1 ± 4.7 to 8.1 ± 4.4
Van de Heyning et al. <sup>24</sup>	Two consecutive open prospective study	Inspire II (Medtronic Inc.)	21(Part 1) 8 (Part 2)	Improvement in AHI from 38.9 ± 9.8 to 10.0 ± 11.0 Significantly improved ESS and FOSQ

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Study	Study design	Device used	Sample size	Findings
Schwartz et al. <sup>26</sup>	Prospective Non randomized uncontrolled trial	Apnex (Medical Inc.)	30	Increase in inspiratory airflow with increasing stimulation intensity
Mwenge et al. <sup>20</sup>	Open-label single arm study	Aura6000TM (ImThera Medical Inc.)	13	Improvement in AHI from 45.2 to 21.0 Improvement in ODI from 29.2 to 15.3 Improvement in the arousal index from 36.8 to 24.9
Strollo et al. (STAR trial) <sup>19</sup>	Prospective single group trail followed by Randomized controlled therapy withdrawal study	Inspire (Medtronic Inc.)	126	Reduction in median AHI score by 68% (29.3 events/h to 9.0 events/h) Reduction in ODI score by 70% (25.4 events/h to 7.4 events/h) Significantly higher AHI score in therapy withdrawal group
Kezirian et al. <sup>21</sup>	Single arm open-label study	Apnex (Medical Inc.)	31	Improvement in AHI from 43.9 to 18.7 in subjects with BMI $\leq$ 35 No significant changes in the subject with BMI > 35 Implant-related adverse events to implantation procedure and therapy in 71% and 32% at 12 months, with serious adverse events in 10%

## RESULTS

Six studies with a total of 242 patients were included in this review. All the studies demonstrated reduction in AHI, ODI and ESS. Despite using different hypoglossal nerve stimulators in each subgroup analysis, no significant difference was found in any of the comparisons, suggesting equivalent efficacy regardless of the system in use.

## DISCUSSION

In 2014, Strollo et al. conducted an uncontrolled cohort study on 126 patients (STAR trial) and reported a 68% decrease in the median AHI score and a 70% reduction in the ODI score.<sup>19</sup> Similar results were reported by Van de Heyning et al. in 2012.<sup>24</sup> Both the studies were conducted using Inspire (Medtronic Inc.) device. In 2012, Schwartz et al. conducted a study on 30 patients using the Apnex (Medical Inc.) device and reported an

increase in inspiratory airflow with increasing stimulation intensity.<sup>26</sup> Similar results were reported by Eastwood et al. in 2011 using the same device.<sup>25</sup> However, Kezirian et al. in 2014, reported implant-related adverse events to implantation procedure and therapy in 71% and 32% subjects 12 months respectively with four patients requiring explantation of the device.<sup>21</sup> In 2013, Mwenge et al. in 2013 used the Aura6000TM (ImThera Medical Inc.) on 13 subjects and reported significant improvement in AHI, ODI and arousal index.<sup>20</sup>

Although CPAP, the standard first-line therapy has proved to be highly effective, suboptimal patient compliance has been shown to limit long-term results in many patients. A universally accepted second-line therapy does not exist. The current treatment plan may include oral appliance therapy, weight loss, positional therapy, lowering nasal resistance, and airway reconstructive surgery—often in combination. Even with this variety of second-line options, many patients remain inadequately treated with residual symptoms and persistent health risks and require an effective option. HGNS therapy has been shown to provide safe and effective short-term management in a cohort of moderate-to-severe OSA patients who were unable to achieve benefit with positive pressure therapy.<sup>27</sup>

The HGNS has several unique advantages compared to traditional OSA surgeries:

- It provides multilevel airway improvement with only one procedure
- Upper airway stimulation therapy is a titratable and adjustable therapy, similar to CPAP or even oral appliances.
- Unlike other surgical procedures that provide a one-time result, hypoglossal nerve stimulation parameters can be modified postoperatively through a variety of configurations to optimize effectiveness as well as patient comfort/adherence.<sup>28</sup>

The HGNS therapy has a very favorable risk-benefit profile and is well-positioned as a salvage treatment for patients with moderate-severe OSA, however further studies are needed on long-term adherence and effectiveness as OSA is a chronic condition. Further, more research is required to study the potential role of UAS therapy in patients with a BMI >32 kg/m<sup>2</sup>. Long-term cost-effectiveness of the therapy needs to be determined. Also, there is a need to define the most effective and appropriate stimulation parameters and titration protocols.

## Complications and Limitations of Hypoglossal Nerve Stimulation

Certain adverse effects have been noticed with HGNS. The most common procedure-related event was numbness/pain at the incision sites. Insomnia and other psychological issues were reported both by Kezirian et al. and Strollo et al. Other common adverse events were, the need for implanted pulse generator and sense lead replacement due to unstable sensing performance and dislodgement of the stimulation lead cuff. Kezirian et al. also reported intermittent tongue soreness in few subjects.<sup>19,21</sup>

Another limiting factor for HGNS therapy is the incompatibility of the current technology with magnetic resonance imaging (MRI) and the need for three external incisions for implantation.<sup>28</sup>

## CONCLUSION

CPAP remains the gold standard therapy for OSA. HGNS therapy has so far proved to be an effective alternative treatment of obstructive sleep apnoea in CPAP intolerant selected group of patients. However, further scientific studies and research projects are required to establish its long-term results, efficacy as well as cost-effectiveness for this therapy.

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